PATENT COOPERATION TREATY

PCT RECEIVED 24 JUL 2006

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/US2005/001630	International filing date *(day/month/year)* 21.01.2005
Priority date *(day/month/year)* 21.01.2004	
International Patent Classification (IPC) or both national classification and IPC A61K38/19, A61P35/04, G01N33/50	
Applicant CHIRON CORPORATION	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later. 1-17-06 11-21-05

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Winger, R

Telephone No. +49 89 2399-8129

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/001630

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-7, 12-25, 28, 29 (industrial applicability)

because:

☒ the said international application, or the said claims Nos. 1-7, 12-25, 28, 29 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	8-25,28,39-42,44-48,50-60
	No:	Claims	1-7,26,27,29-38,43,49,61-64
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-64
Industrial applicability (IA)	Yes:	Claims	8-11,26,27,30-64
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Section III

1. Claims 1-7, 12-25, 28 and 29 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

2. The term "mutein" used in the claims is vague and unclear and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of the claims unclear, Article 6 PCT.

Re Section V

3. Prior Art: Reference is made to the following documents cited in the International Search Report
   - D1: WO 2004/045532 A
   - D2: DATABASE WPI Section Ch, Week 200171 Derwent Publications Ltd., London, GB; Class B04, AN 2001-613857 & JP 2001 233784 A
   - D3: WO 98/39449 A
   - D4: EP-A-0 955 056
   - D5: WO 90/01942 A
   - D6: EP-A-0 955 365
   - D7: MIYAMOTO TAKESHI ET AL: "Differentiation and function of osteoclasts." THE KEIO JOURNAL OF MEDICINE. MAR 2003, vol. 52, no. 1, pages 1-7

3.1 Document D1 discloses the information of the current application. Assuming the priority to be valid document D1 does not constitute prior art for the international phase.

3.2 Document D2 discloses that M-CSF suppresses bone metastases.

3.3 Document D3 discloses a method for reducing the population of diseased cells using a M-CSF mutant, especially for the treatment of cancer and possibly in combination with another cancer therapeutic agent (e.g. gancyclovir). Metastatic cancers may also be treated. Document D4 discloses the use of CSF-1 (along with muteins) for the treatment of metastases alone or in combination with IFNγ. Document D5 discloses that M-CSF (and variants) causes reduction in metastases.

3.4 Document D6 discloses the design of M-CSF muteins as M-CSF antagonists.

3.5 Document D7 discloses osteoclasts are formed in the presence of M-CSF and are

responsible for bone destruction induced by metastatic tumors. Inhibition of osteoclast formation prevents bone metastasis.

4. Novelty (Article 33(2) PCT):

4.1 Claims 1-7, 29-38 and 61-64 relate to methods of treating metastatic bone cancer using M-CSF muteins. However, in view of the vague term "mutein" document D2 seems to anticipate the subject-matter of said claims.

4.2 Claims 8-13 relate to a method of screening for M-CSF muteins using osteoclasts. As none of the prior art documents disclose such a method the subject-matter of said claims seems to be novel.

4.3 Claims 14-25, 28, 39-42, 44-48 and 50-60 relate to methods of treating metastatic bone cancer using M-CSF muteins in combination with a further therapeutic agent or method. As none of the prior art documents disclose such a method the subject-matter of said claims seems to be novel.

4.4 Claims 26, 27, 43 and 49 relate to a pharmaceutical composition comprising a M-CSF mutein and a cancer agent or instructions for a combined use. Such compositions seem to be anticipated by at least documents D2-D4.

5. Inventive Step (Article 33(3) PCT):

5.1 Documents D3-D5 all disclose the use of M-CSF muteins for the treatment of metastatic cancer both alone or in combination with other anti-cancer agents. Therefore, the arbitrary selection of a specific metastatic cancer, i.e. the subject-matter of claims 1-64, does not seem to be inventive.

5.2 Starting from D7 as the closest prior art, which discloses the involvement of M-CSF in metastatic bone tumor, the problem to be solved can be regarded as to provide inhibitors of M-CSF for preventing bone metastases. However, as document D6 anticipates the use of M-CSF muteins as antagonists, the subject-matter of claims 1-64 does not seem to be inventive.